RESEARCH PAPER

Design And Development Of Floating Pulsatile Drug Delivery System Of Domperidone

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Abstract
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Keywords: NA.
How To Cite This Article: Sambathkumar R, Kannan C, Radhakrishnan S, Priya P, Sundarraj P. Design and development of floating pulsatile drug delivery system of domperidone. Int J Drug Deliv Technol. 2026;16(9s): 849-866; Doi: 10.25258/Ijddt.16.9s.89

1. INTRODUCTION:

A circadian rhythm is a naturally occurring physiological process that occurs approximately every 24 hours and controls the sleep-wake cycle. As the body's internal biological clock, it optimizes processes like hormone release, body temperature, and metabolism by coordinating changes in the body, mind, and behavior with the daily light-dark cycle.[1,2]

Since the body's circadian clock controls many physiological and hormonal functions throughout the day, it has a significant impact on the emetic response (vomiting and nausea). Disorders such as cyclic vomiting syndrome (CVS) usually cause vomiting episodes that occur on a daily basis and are connected to the internal clock of the body that regulates gastrointestinal and autonomic processes[3,4]. Time-specific vomiting peaks in certain conditions can be explained by the circadian fluctuations of hormones including growth hormone, prolactin, and cortisol, which impact the brain-gut axis and change susceptibility to nausea triggers.[5]. Additionally, circadian rhythms regulate gastrointestinal motility and secretion, essential in the emetic reflex [6]. Clinical reports of nausea brought on by chemotherapy provide more evidence that the best antiemetic treatment can be guided by timing that is dependent on circadian rhythms.

Pharmaceutical research has greatly advanced with the introduction of drug delivery methods that offer controlled and site-specific release, particularly for medications that require chronotherapy or have limited absorption windows. Building on this, chronopharmaceutics is concerned with designing drug delivery systems that allow for the regulated and timed release of medications to correspond with the varying nature of disease symptoms by synchronizing drug release with the body's biological rhythms. The gastroretentive floating pulsatile tablet system is a perfect illustration of this strategy. [7].

Specialized oral dosage forms known as "pulsating floating tablets" are made to release antiemetic medications (such domperidone) in a precise "pulse" following a predetermined lag period, as opposed to a continuous sustained release. For ailments like nausea and vomiting, which frequently worsen at predictable times in relation to cardiac or gastric rhythms, these systems can maximize treatment for symptoms that follow a circadian rhythm (biological timing) 8.

These systems are especially helpful for conditions like gastrointestinal problems, which are governed by circadian rhythms and benefit from medications that are released early in the morning to maximize therapeutic efficacy and minimize side effects.[9]

Domperidone is an antiemetic dopamine antagonist that has restricted bioavailability because of its

significant first-pass metabolism and poor solubility at gut pH. As a result, creating a gastro-retentive floating system can greatly lengthen its stay in the stomach, improving absorption and therapeutic results. In order to prolong gastric retention without interfering with normal gastrointestinal motility, floating medication delivery systems use low-density polymers or effervescent chemicals that produce gas to keep the dosage form afloat.[10,11,12]

For medications like domperidone that need to be released at a specific time to align with the pathophysiology or peak of symptoms, pulsatile release inside a floating system provides the benefit of delayed drug release following stomach retention. Domperidone's floating time and drug release kinetics have been effectively optimized using a variety of polymers, including sodium bicarbonate, polyethylene oxide (PEO), and hydroxypropyl methylcellulose (HPMC). This allows for the customization of lag time and sustained release patterns.[13s]

Customizable floating pulsatile tablets with controlled lag times that vary from 30 minutes to several hours have been developed recently through the use of innovative fabrication techniques like hot-melt extrusion in conjunction with 3D printing. This has improved patient compliance and therapeutic efficacy. These developments provide low-cost, customizable dose formulations with less adverse effects, promising personalized medicine.[12] The aim of the present work was to the development of a pulsatile drug delivery system of Domperidone for the effective treatment of emetic and Cyclic vomiting syndrome.

2. MATERIALS

The list of materials used in this study includes Domperidone supplied by Sri Krishna Pharmaceuticals; Crospovidone obtained from Star-Tech and JRS Speciality Products Co. Ltd; Lactose from DFE Pharma; Sodium bicarbonate from Avantor Materials India Limited; Povidone K30 supplied by JH Nanhang Life Sciences Co. Ltd; Citric acid from Sunil Chemicals; Aerosol sourced from Cabot Sanmar Limited; Magnesium stearate provided by Amishi Drugs & Chemicals Private Limited; HPMC K4M from Colorcon Asia Pvt. Limited; HPMC K100M from Lotte Fine Chemical Co. Ltd.; Carbopol supplied by Lubrizol; Ethyl cellulose sourced from Taian Ruitai Cellulose Co. Ltd.; and Microcrystalline cellulose 112 from Wei Ming Pharmaceutical MFS. Co. Ltd. All materials were procured from reputable manufacturers and suppliers to ensure the quality and reproducibility of the pharmaceutical formulation process.

3. METHODOLOGY

3.1. PRE-FORMULATION PARAMETERS:

Pre-formulation study is the first step in developing a suitable dosage form of a drug, involving investigation of its physical and chemical properties alone and with excipients to ensure stability and bioavailability. The characterization of pure drug includes evaluation of organoleptic properties such as colour, odour, and taste. Solubility studies are conducted in various solvents and pH conditions to identify the best formulation approach. The melting point of Domperidone was determined by the open capillary method, where the drug-filled capillary tube was gradually heated in a melting point apparatus, and the temperature at which melting began was recorded.[14,15,16]

3.2. PREPARATION OF STANDARD CALIBRATION CURVE OF DOMPERIDONE:

3.2.1. SELECTION OF COMMON SOLVENT:

The selection of common solvent was made after assessing the solubility of the drug in different solvents. The drug was found to be completely soluble in Organic Solvents such as DMSO, DMF, and Methanol.[17]

3.2.2. STOCK SOLUTION:

60 mg of Domperidone Maleate working standard was dissolved in 100 ml volumetric flask and 50 ml of 0.1 N HCL was added to make up the volume.

3.2.3. STANDARD SOLUTION:

2.5 ml of stock solution was diluted to 100 ml with 0.1 N HCL. Similarly, 4.0 ml, 5.0 ml, 6.0 ml, and 7.5 ml of standard solution was taken and make up the volume with 0.1 N HCL. UV absorbance was taken at the wavelength of 286 nm in UV-visible spectrophotometer UV-1601. [18]

4. DRUG-EXCIPIENT/ COMPATIBILITY STUDIES:

Before formulating a drug substance into a dosage form, it is essential to ensure chemical and physical compatibility. Compatibility studies provide information about the drug's nature and guide the selection of suitable excipients or carriers for formulation. In this work, infrared spectrophotometry was used to detect possible chemical interactions between the drug and excipients.

One milligram of the sample was triturated with 300 mg of potassium bromide in a mortar. A small amount of this mixture was compressed into a pellet at 1000 kg/cm² using a pellet maker. The pellet was scanned from 4000 cm^{-1} to 400 cm^{-1} using a Shimadzu FT-IR spectrophotometer. The pellet was made by gradually adding the mixture to the press's bottom under high pressure and carefully extracting it. The collected spectra were analyzed to identify any interactions,

bond formation, or absence of effects between the drug and excipients.

The chosen drugs and excipients were screened for compatibility using the ATR-FTIR method. The resultant spectra were compared for any changes, focusing on characteristic peaks of the respective functional groups. [19,20]

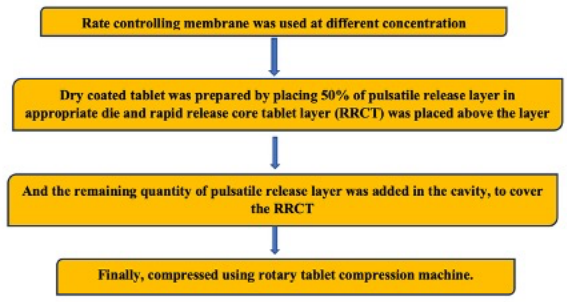
5. FORMULATION OF RAPID RELEASE CORE TABLET:

The floating pulsatile release tablet will be prepared by the wet granulation method as follows: The active pharmaceutical ingredients, crospovidone, and lactose are sifted through #40 and blended together. This blend is mixed in a polyethylene bag for 10 min. A binder solution is prepared and poured over the dry mix, followed by mixing. The granules are dried in a hot air oven at 60°C for 1 hour and then passed through #30. Citric acid and sodium bicarbonate are shifted through #40 and added to the granules. Aerosols are shifted through #60 and blended in. Magnesium stearate and coloring agent, sifted through #60, are added and mixed in a polyethylene bag for 10 min. The blend is then compressed with 6.35 mm punches based on the average weight (100 mg) of the core tablet.[21,22]

Table 1: Formulation of Domperidone

INGREDIENTS (mg)	Trial-1	Trial-F2	Trial-F3	Trial-F4	Trial-F5
DOMPERIDONE (API)	30	30	30		
CROSPOVIDONE	--	3.5	2.5		
LACTOSE	25.5	29.5	25		
POVIDONE	4	5.5	3		
CITRIC ACID	20	25	15		
SODIUM BICARBONATE	15	--	20		
AEROSOL	2	2.5	3		
MAGNESIUM STEARATE	2	2.0	1.5		
FERRIC OXIDE RED	1.5	2.0	2		
PURIFIED WATER	QS	QS	QS		
TOTAL WEIGHT (mg)	**100**	**100**	**100**		

6. PREPARATION OF PULSATILE RELEASE TABLET: [23]



TOP LAYER:

Table 2: Top layer

Polymer and lubricants	F1	F2	F3	F4	F5
HPMC K100M	40	60	50	60	50
HPMC K4M	--	20	--	--	10
SODIUM BICARBONATE	30	10	20	20	15
MICROCRYSTALLINE CELLULOSE 112	10	--	20	10	15
ETHYLCELLULOSE	20	10	10	10	10
TOTAL WEIGHT(g)	**100**	**100**	**100**	**100**	**100**

BOTTOM LAYER:

Table 3: Top layer

Polymer and lubricants	F1	F2	F3	F4	F5
HPMC K100M	30	25	20	30	20
HPMC K4M	10	5	20	--	10
SODIUM BICARBONATE	10	30	20	18	20
ETHYLCELLULOSE	18	10	26	30	28
MICROCRYSTALLINE CELLULOSE 112	10	18	10	10	10
CITRIC ACID	20	10	18	10	10
QUINOLINE LAKE YELLOW	2	2	2	2	2
TOTAL WEIGHT(g)	**100**	**100**	**100**	**100**	**100**

7. DESIGN OF EXPERIMENT AND OPTIMIZATION 24,25,26

Design of experiments (DOE) is a systematic method to determine the relationship between factors affecting a process and its output, essentially finding cause-and-effect relationships. This helps manage process inputs to optimize the output.

Controllable input factors (x factors) are input parameters that can be modified, such as polymer concentration and binder concentration. Responses

(output measures) gauge the desired effect, such as dissolution and disintegration.

DOE aims to describe and explain variation by introducing changes in preconditions, represented by independent variables (input variables or predictor variables). The changes in independent variables are hypothesized to affect dependent variables (output variables or responses). Control variables are held constant to prevent external influence.

Experimental design involves selecting suitable independent, dependent, and control variables, and planning experiments under statistically optimal conditions within resource constraints. Various approaches exist to determine design points (unique combinations of independent variable settings).

Input Variables: Also called factors or independent variables, these can be changed; e.g., excipients, concentrations.

Output Variables: Also called responses or effects, these depend on input variables; e.g., hardness, dissolution time.

Dependent variables depend on the independent variables per some rule or function, while independent variables do not depend on others in the experiment. The variation studied is in dependent variables by altering inputs (regression).

Constraints limit possible values for decision variables in optimization models, categorized as linear (linear combinations within bounds) or nonlinear (arbitrary functions within bounds). Constraints have properties like Name, Lower Bound, Upper Bound, and Value (post optimization). They are implemented by corresponding classes in software and accessed by names or position.

7.1 DOE Software:

Design-Expert® software is best in class for design of experiments, making R&D easy with a user-friendly interface and amazing graphics. It provides powerful tools to design ideal experiments on processes, mixtures, or combinations of factors and components. In this work, we used StatEase DOE Software to leverage these capabilities for efficient experimental design.

7.1.1 Selection of suitable design:

We will discuss fold-over designs that provide the ability to free main effects from two-factor interactions or to de-alias a main effect and all of its two-factor interactions from other main effects and two-factor interactions. This technique involves augmenting the original design with additional runs, often by reversing the signs of factor levels, which helps separate confounded effects and achieve clearer interpretation of the main effects and interactions.

Factors:

Table 4: Types of Constraints

FACTORS	GOAL	LOWER LIMIT	UPPER LIMIT
HPMC	Is in range	30	40
Sodium bicarbonate	Is in range	15	25
Ethylcellulose	Is in range	20	30

Responses:

Table 5: Types of Responses

RESPONSE	GOAL	LOWER LIMIT	UPPER LIMIT
Floating time	Is target 9.25	6	12.5
In-vitro dissolution	Is target 9.25	6	12.5

Constraints

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:HPMC+	is in range	30	40	1	1	3
B:Sodiumbicarbonate	is in range	15	25	1	1	3
C:EC	is in range	20	30	1	1	3
DIsso Time	is target = 9.25	6	12.5	1	1	3
StdErr(DIsso Time)	minimize	0.3629	1.02644	1	1	3
Floating time	is target = 9.25	6	12.5	1	1	3
StdErr(Floating time)	minimize	0.3629	1.02644	1	1	3

Fig 1. Selection of appropriate constraints by StatEase software

7.1.2. Analysis of Variance (ANOVA) and Visualization Techniques in Experimental Design:

Analysis of variance (ANOVA) is a statistical tool that splits observed variability in data into systematic factors, which influence the data, and random factors, which do not. It assesses the impact of independent variables on dependent variables, often using Fisher's test. ANOVA evaluates model significance, with a non-significant lack of fit indicating a good model fit. R^2 values show how well the model estimates the response. ANOVA results can be visualized through contour plots, which graphically represent 3D surfaces in 2D, showing constant response values (iso-lines) across independent variable grids. DOE contour plots assist in visualizing complex experimental designs, with many software offering these capabilities to analyze and optimize formulations by interpreting 3D response surfaces. [28]

8. EVALUATIONS:

8.1. MICROMERITIC PROPERTIES OF CORE TABLET:

8.1.1. FLOW PROPERTIES MEASUREMENTS:

The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. The flow property measurements include bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose. The flow property measurements of drugs and blends were determined to select the type of granulation technique to be carried out for the formulation.

8.1.2. BULK DENSITY (pb):

The bulk density of the granules was determined by pouring gently 30 gm of sample through a glass funnel into a 50 ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density will be calculated as follows,

$\rho_b = M / V_b$

M = mass of the powder

V_b = Bulk volume of the powder [29,33]

8.1.3. TAPPED DENSITY (pt):

30 grams of granule sample was poured gently through a glass funnel into a 50ml graduated cylinder. The cylinder will be tapped from a height of 2 inches until a constant volume will be obtained. Volume occupied by the sample after tapping will be recorded and tapped density will be calculated as follows,

$\rho_t = M / V_t$

M = mass of the powder

V_t = tapped volume of the powder [30.]

8.1.4. CARR'S INDEX (OR) % COMPRESSIBILITY (CI) :

It indicates powder flow properties. It is measured to determine the relative importance of interparticulate interactions. It is expressed in % and is given by,

$$CI = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

ρ_t = tapped density

ρ_b = bulk density [31.]

8.1.5. HAUSNER'S RATIO:

Hausner's ratio is defined as a ratio of a tapped density to bulk density. It is a measure of relative importance of interparticulate interactions [31.]

$HR = \rho_t / \rho_b$

8.1.6. ANGLE OF REPOSE (θ):

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The prepared granules were allowed to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of the granules from the funnel mouth forms a pile of granules at the surface this is continued until the pile touches the stem tip of the funnel. A rough circle is drawn around the pile base and the radius of the granule cone was measured. Angle of repose was then calculated with the use of the following formula,

$\theta = \tan^{-1} (h / r)$

θ= angle of repose

h= height of the pile

r = average radius of the powder cone [32,33]

Table 6: Flow properties of the powder 29,30,34

Flow Character	Compressibility index	Hausner's ratio	Angle of repose
Excellent	<10	1.00-1.11	21-30
Good	11-15	1.12-1.18	31-35
Fair	16-20	1.19-1.25	36-40
Passable	21-25	1.26-1.34	41-45
Poor	26-31	1.35-1.45	46-55
Very poor	31-38	1.46-1.59	56-65
Very very poor	>38	>1.60	>66

9. POST-COMPRESSION PARAMETERS:

9.1. WEIGHT VARIATION TEST:

20 tablets were randomly chosen from each tablet formulation and individually weighed to check for weight variation. According to IP, the weight variation specification is mentioned in Table Not more than 2 of the individual weight of tablets out from the average weight by more than the percentage deviation and none deviate by more than twice the percentage.[35]

Table 7: Weight variation specification as per IP

AVERAGE TABLET WEIGHT	% DEVIATION ALLOWED
80 mg or less	±10
80 mg to 250 mg	±7.5
250 mg or more	±5

9.2. HARDNESS TEST:

Tablet hardness or crushing strength is the force applied across the diameter of the tablet to break it. The resistance of tablets towards abrasion, breakage or chipping, under transportation conditions, handling and storage before use depends on its hardness. Tablet hardness was determined for each formulation by Pfizer hardness tester. It was expressed in kg/cm^2 .[36]

9.3. THICKNESS:

The thickness of the prepared tablets was determined for 3 pre-weighed tablets from each formulation utilizing Vernier calliper, expressed as average

thickness in mm. Tablet thickness must be within ±5% variation of the standard.[35]

9.4. FRIABILITY:

The friability test was performed employing Roche friabilator to assess the effect of shocks and friction, which may cause tablet chipping, capping or breakage problems. A prior weighed sample of tablets was taken in the plastic chamber of friabilator that revolves at a speed of 25 rpm for 4 mins and the tablets were dropped at a distance of 6 inches with each revolution. Tablets after the friability test were de-dusted and re-weighed. The core tablets must not lose >1% of their weight.[37]

$$\% \text{ friability} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

9.5. DISINTEGRATION TIME:

The disintegration test was carried out as described under the procedure for core tablets in USP. One tablet will be placed in each of the six tubes of the basket of the assembly. The apparatus was operated for one hour using simulated gastric fluid, maintained at 37 ± 2°C as the immersion fluid. After 1 hour the tablet will be examined for disintegration, cracking, and softening. Then the apparatus was operated for a specified time. [38,39,40]

9.6. IN-VITRO DISSOLUTION METHODS FOR CORE TABLETS:

9.6.1. DISSOLUTION PARAMETERS:

Medium : 0.1M Hcl
Apparatus : USP type-2 Paddle
RPM : 50
Temperature : 37± 0.5°C
Volume : 900 ml
Equipment : UV-visible spectrophotometer
Wavelength : 286 nm
Time : 45 Minutes

9.6.2. PROCEDURE:

The dissolution test apparatus was kept as per the above conditions. Add 900 ml of dissolution in to 6 individual vessels and after reached the desired temperature drop 6 individual tablets into the dissolution vessel. Withdraw 15 ml of sample from each vessel and filter. (Use Chromafil Xtra Syringe Filter, GF - 1.0 µm) Discard first 5 ml of the filtrate and use the filtrate for analysis.

Measure the absorbance of the sample preparation and standard preparation at a maximum of 286 nm [41,42].

10. EVALUATION OF FLOATING PULSATILE RELEASE TABLET:

10.1. THICKNESS:

The thickness of the tablet is important for the uniformity of tablet size. Thickness was measured using vernier calipers and it is expressed in millimeters. It was determined by checking the thickness of ten tablets of each formulation. ±5% may be allowed depending on the size of the tablet.[43]

10.2. HARDNESS TEST:

Tablets require a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing, and shipping. The hardness of the tablet was measured using. The hardness is measured in terms of kg/cm². 10 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded. [43,44]

10.3. FRIABILITY:

10 tablets were weighed and the initial weight of these tablets were recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. The tablets were then removed from the friabilator, dusted off the fines and again weighed and the weight was recorded. Percentage friability was calculated by using the formula. [43,44]

$$\textbf{Friability (\%)= W1-W2/W1× 100}$$

10.4. SWELLING INDEX:

The swelling index , in the context of pharmaceutical tablets, is a measure of the extent to which a tablet can absorb liquid and swell when placed in a dissolution medium. This parameter is particularly important for floating and sustained-release tablets, as the swelling behaviour influences the tablet's buoyancy , drug release, and overall performance [45].

Swelling index (%) = (Weight after swelling - Initial weight)/ Initial weight x 100

10.5. LAG TIME

Lag time was considered as the time when the tablet burst and core tablet is out of press coating. This is considered as predetermined off-release period.

10.5.1 *IN-VITRO* BUOYANCY STUDIES:

The ***in vitro*** buoyancy was characterized by floating lag time and total floating time. The test was performed using USP type II apparatus at 50 rpm in 900 ml of 0.1N HCL (pH 1.2) maintained at 37±0.5°C. The time required for the tablet to rise to the surface of the dissolution medium and the duration of time the tablet constantly floats on the dissolution medium were noted as floating lag time and total floating time, respectively.[46]

10.5.2. IN-VITRO DISSOLUTION METHODS FOR FLOATING PULSATILE RELEASE TABLETS:

In-vitro Dissolution studies of Pulsatile delivery systems will be done with the conventional paddle method of press-coated tablets were performed at 37°C ±0.5°C using 0.1N Hcl in USP II paddle method at 50 rpm 15 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 15 ml of fresh buffer maintained at the same temperature upto 12 hours.

The samples will be analyzed at 286 nm using a UV spectrophotometer. The lag time and percentage release will be determined for each formulation.[47]

10.6. ASSAY (BY HPLC)

Chromatographic Conditions:

Column : C18, 10 cm × 4.6 mm, 3 µm

Column Temperature : Ambient

Flow rate : 1.5 ml / min

Detection wavelength : 280 nm

Injection volume : 10 µl

Autosampler Temperature : 15°C

Elution : By Gradient

Diluent : 0.01 M hydrochloric acid : Methanol (50 :50)

Mobile phase A : 0.5% w/v solution of ammonium acetate

Mobile phase B : Methanol

Preparation of 0.5% w/v solution of ammonium acetate :Dissolve 5 g of ammonium acetate in 1000 ml of water.

Preparation of 0.01 M hydrochloric acid : Dissolve 0.85 ml of hydrochloric acid in 1000 ml of water

Table 8: Gradient Program

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)
0	60	40
10	5	95
12	5	95
14	60	40
24	60	40

NOTE

Equilibrate the column for at least 30 minutes with methanol and equilibrate with the initial mobile phase for at least 5 minutes.

10.6.1. STANDARD SOLUTION

Weigh accurately about 26.0 mg of Domperidone Maleate working standard in a 200 ml volumetric flask, dissolve and make up to the volume with the mixture of equal volumes of 0.002 M hydrochloric acid and methanol.

10.6.2. TEST SOLUTION

Transfer 10 whole tablets in 500 ml volumetric flask, add 300 ml of methanol, shake well for 10 minutes, mix with the aid of ultrasound for 20 minutes. Make upto the volume with methanol and filter. Discard first 3 ml of the filtrate. (Use Chromafil Xtra Syringe Filter, GF - 1.0 µm) To 17 ml of the filtrate add 1 ml of 0.1 M hydrochloric acid and sufficient water to produce 100 ml.[48,49.]

11. STABILITY STUDIES:

The stability studies will be carried out of the most satisfactory formulation as per ICH guidelines to assess the drug and formulation stability. The most satisfactory formulation sealed in aluminium packaging and kept in humidity chamber maintained at for one month. At the end of studies, samples will be analysed for the post compression parameters like average weight, thickness, diameter, hardness, DT, dissolution and drug content. [50,51,52.]

Table 9: ICH guidance description for stability study of pharmaceutical formulation

Study duration	Storage conditions	Minimum period
Accelerated	40°C ± 2 °C / 75% RH ± 5%	6 months
Long term	30°C ± 2 °C /75% RH ± 5% RH	12 months

12. RESULTS AND DISCUSSION

12.1 PREFORMULATIONSTUDIES

12.1.1 CHARACTERIZATION OF PURE DRUG (API)

12.1.1.1 DESCRIPTION

- **COLOUR:** White or almost white powder
- **ODOUR:** Odourless
- **TASTE:** Extremely bitter taste.

12.1.1.2 SOLUBILITY STUDIES

Table 10: Solubility studies of Domperidone

S.no	Solvent	Sparingly soluble	Slightly soluble	Very Slightly soluble
1.	Dimethyl formamide	+	-	-
2.	Water	-	-	+
3.	Ethanol	-	-	+

4.	Methanol		+	-
5.	HCL	+	-	-

The solubility of Domperidone was determined in different solvents such as water, Dimethyl formamide, ethanol, HCL, and methanol and it is observed that the pure drug is Very Slightly soluble in water, ethanol and sparingly soluble in HCL, Dimethyl formamide and slightly soluble in methanol.

12.1.1.3 DETERMINATION OF MELTING POINT

The melting point of the pure drug Domperidone was determined by an open capillary method. The melting point of the Domperidone was found to be 242.9°C. Thus, the melting point indicates the purity of the drug.

12.1.1.4 STANDARD CALIBRATION CURVE OF DOMPERIDONE:

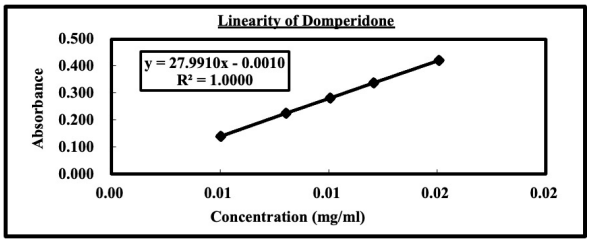
The linearity of the UV method was demonstrated for Domperidone Maleate equivalent to Domperidone solutions ranging from 0.005030 mg/ml to 0.015090 mg/ml, which is equivalent to 50% to 150% of the Domperidone working strength. Five standard solutions at concentrations within the mentioned range were prepared and analyzed as per the method.

The linearity results obtained are shown in Table 13. Figure 34 shows the line of best fit for absorbance versus concentration of Domperidone.

Table 11: Linearity of Domperidone

Level	% of Domperidone w.r.t. working strength	Concentration (mg/ml)	Absorbance
50%	50.3	0.005030	0.140
80%	80.5	0.008050	0.224
100%	100.6	0.010060	0.280
120%	120.7		
150%	150.9		
Correlation Co-efficient			

Figure 2: Linearity graph for Domperidone



Thus, the UV method for the dissolution of Domperidone in Domperidone Tablets was shown to be linear in the range of 50% to 150% of the working concentration with a Correlation Coefficient of 1.0000. The range of the UV method for determining the dissolution of Domperidone in Domperidone Tablets is 50% to 150% of the working strength.

13. DRUG - EXCIPIENT COMPATABILITY STUDIES:

The FTIR spectra of the pure drug, excipient and physical mixture of drug and excipients used in floating controlled tablet formulation in fig were recorded in between 400- 4000 wave number (cm^{-1}).

Figure 3: FTIR studies of pure drug Domperidone

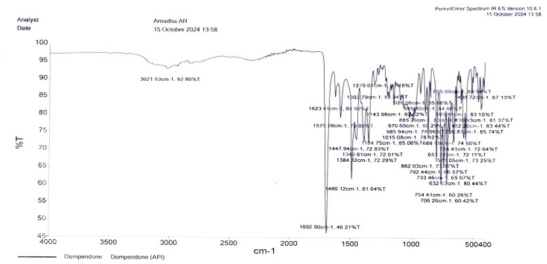


Table 12: FT-IR interpretation of pure Domperidone

S.no	Functional group	Standard IR range cm^{-1}	Assessment peaks of pure drug cm^{-1}
1	Aromatic (C=C)	1700 – 1400	1692.80, 1579.26,
2	Secondary alcohol	1350 – 1260	1346.61, 1270.01
3	Alkenes	1000 – 650	985.94, 862.03, 792.44, 754.41, 706.26, 688.99,

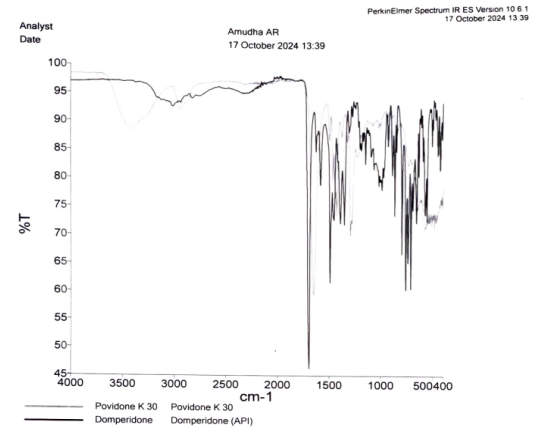


Figure 4: FTIR studies of Domperidone with excipient povidone

S.no	Functional group	Standard IR range cm^{-1}	Assessment peaks of pure drug cm^{-1}
1	Secondary amine (N-H	3500 – 3300	3409.23
2	Aromatic (C=C)	1700 – 1400	1646.51, 1493.01, 1461.17,
3	Secondary alcohol	1350 – 1260	1317.51, 1287.14

Table 13: FT-IR interpretation of Domperidone and povidone

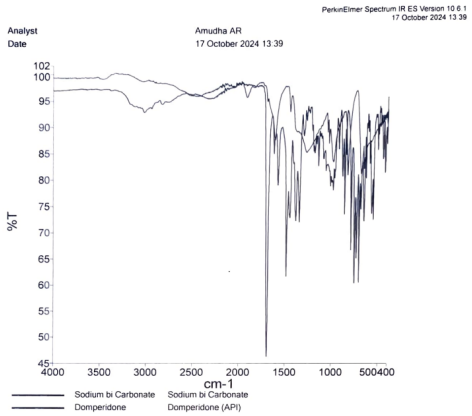
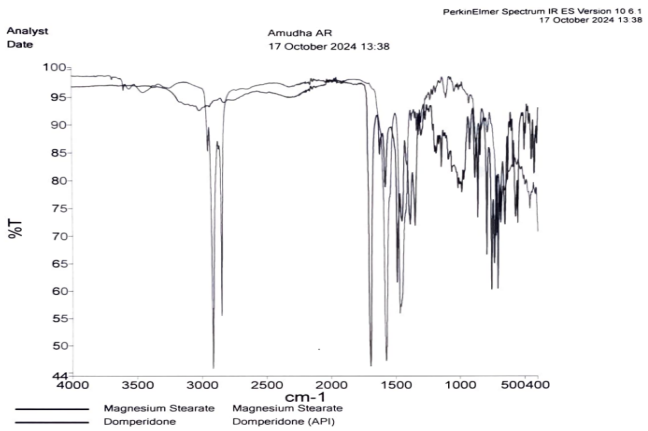


Figure 5: FTIR studies of Domperidone with sodium bicarbonate

S.no	Functional group	Standard IR range cm^{-1}	Assessment peaks of pure drug cm^{-1}
1	Aromatic (C=C)	1700 – 1400	1612.40, 1450.03
2	Secondary alcohol	1350 – 1260	1270.99
3	Alkenes	1000 – 650	984.17, 830.58, 686.45,

Table 14: FT-IR interpretation of Domperidone and sodium bicarbonate

Figure 6: FTIR studies of Domperidone with magnesium stearate



S.no	Functional group	Standard IR range cm^{-1}	Assessment peaks of pure drug cm^{-1}
1	Secondary amine (N-H	3500 – 3300	3453.94
1	Aromatic (C=C)	1700 – 1400	1571.40, 1463.81
2	Secondary alcohol	1350 – 1260	1336.65, 1321.27
3	Alkenes	1000 – 650	790.29, 722.01, 685.01

Table 15: FT-IR interpretation of Domperidone with magnesium stearate

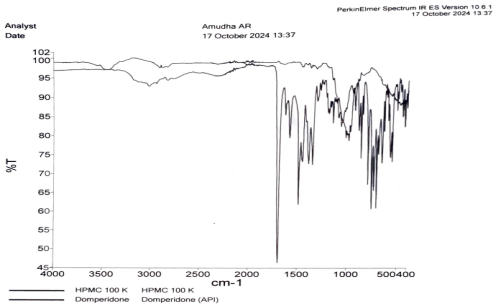


Figure 7: FTIR studies of Domperidone with HPMC K100M

S.no	Functional group	Standard IR range cm^{-1}	Assessment peaks of pure drug cm^{-1}

1	Secondary amine (N-H Stretching)	3500 – 3300	3442.04
2	Alkenes	1000 – 650	945.81

Table 16: FT-IR interpretation of Domperidone and HPMC K100M

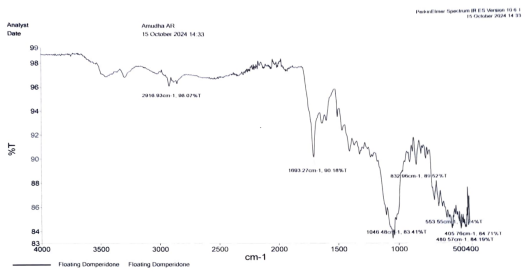


Figure 8: FTIR of optimized formulation (F4)

The FT-IR study was performed using Fourier transform infrared spectroscopy. The FTIR spectrum of Domperidone was found to be in the wave numbers such as 1346.61 showing secondary alcohol, 1692.80 showing aromatic, and 792.44 showing alkenes.

The FTIR spectrum of Domperidone and excipient povidone was found to be in the wave numbers such as 3409.23 showing N-H stretching, 1422.39 showing aromatic, and 1287.14 showing secondary alcohol.

The FTIR spectrum of Domperidone and excipient sodium bicarbonate was found to be in the wave numbers such as 1450.03 showing aromatic, 1270.99 showing secondary alcohol, 655.87 showing alkenes.

The FTIR spectrum of Domperidone and excipient magnesium stearate was found to be in the wave numbers such as 3453.94showing N-H stretching 1571.40 showing aromatic, 1321.27showing secondary alcohol, 685.01showing alkenes.

The FTIR spectrum of Domperidone and excipient HPMC K100M was found to be in the wave numbers such as 3442.04 showing secondary amine N-H stretching and 945.81 showing alkenes.

13.1. PRECOMPRESSION STUDY:

Table 17: Evaluation of flow properties of API & Granules:

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Hausner's ratio	Compressibility index (%)	Flow properties
API	0.62	0.75	34.79	1.20	17.33	Good
Trial-1	0.857	0.909	27.52	1.060	5.72	Excellent
Trial-2	0.882	0.937	22.12	1.062		
Trial-3	0.937	1.034	33.05	1.103		
Trial-4	0.967	1.071	27.88	1.107		
Trial-5	0.909	0.9677	23.65	1.064		

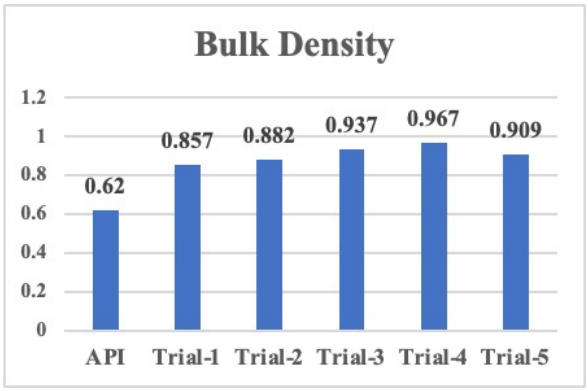


Fig 9: Bulk Density

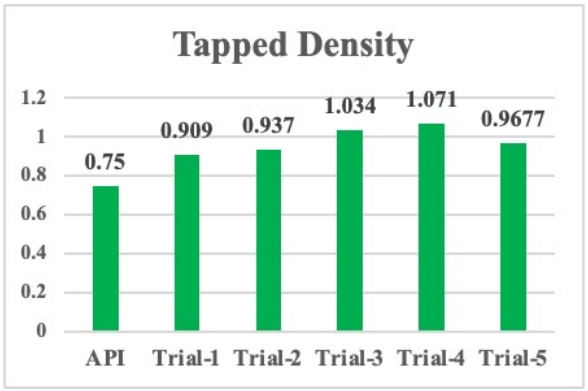


Fig 10: Tapped Density

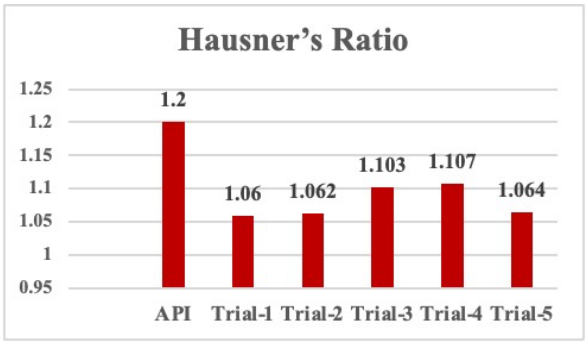


Fig 11: Compressibility index

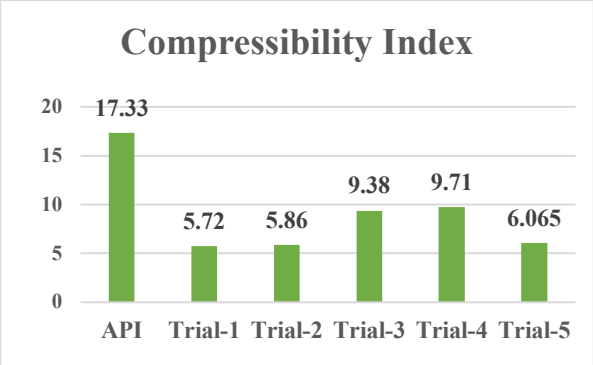
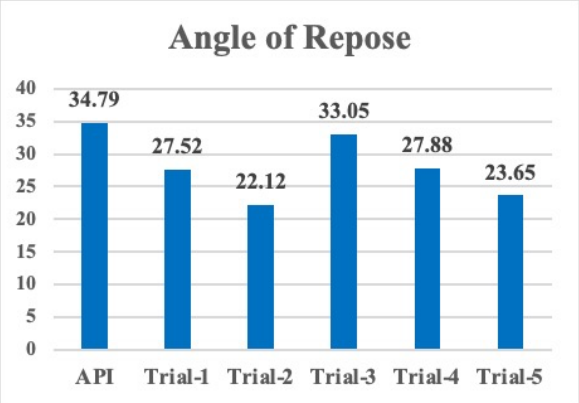


Fig 12: Hausner's Ratio

Fig 13: Angle of repose



The bulk density of Domperidone API and blend ranged from 0.62 g/ml to 0.967 g/ml and the tapped density ranged from 0.909 g/ml to 1.071 g/ml. The API and blend compressibility index ranges from 5.72 % to 17.33 %, and Hausner's ratio ranges from 1.060 to 1.20. The angle of repose ranges from 22.12 to 34.79. Hence the entire formulation trial API and blend was found to be good and have Excellent flow properties.

14. POST COMPRESSION EVALUATION

14.1. Evaluation of core tablets:

The formulation of rapid-release time-controlled core tablets of Domperidone was evaluated for post-compression parameters. The results of weight variation, thickness, hardness, friability, and disintegration time are given in table

Table 18: Evaluation of core tablets

Formulation	Weight Variation (%) (±SD)	Thickness (mm) (±SD)	Diameter (mm)	Hardness (kg/cm2)	Friability (%)	Disintegration (Sec)
Trial-1	98.75 ± 0.15	2.68 ± 0.05	6.35	8.65 ± 0.08	0.50	185± 5
Trial-2	100 ± 0.64	2.88 ± 0.06	6.35	8.73 ± 0.10	0.56	173± 3
Trial-3	99.69± 0.16	2.63 ± 0.09	6.35	8.69 ± 0.06	0.49	171± 6
Trial-4	100.03± 0.03	2.83 ± 0.02	6.35	8.96 ± 0.15	0.71	150 ± 4
Trial-5	102.05± 0.88	2.81 ± 0.04	6.35	7.95 ± 0.06	0.63	137± 3

Weight variation:

The percentage weight variations for all formulations were tabulated in (Table 20). The formulated batches passed the weight variation test as the Percentage weight variation was within the pharmacopoeial limits.

Thickness:

The measured thickness of tablets of each batch ranged between 2.88 ± 0.06 to 2.63 ± 0.09mm. The value shows that formulated tablets have a uniform thickness. The parameters were reported in (Table 20)

Hardness:

The measured hardness of tablets of each batch ranged between 7.95± 0.15 to 8.96± 0.06 Kg/cm^2. This ensures good handling characteristics of all batches. The results were shown in (Table 20)

Friability:

The values of the friability test were tabulated in (Table 20). The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Disintegration time:

The disintegration time of all the batches was found between 137± 3 seconds to 185± 5seconds and the results are shown in (Table 20). The effects of independent variables on disintegration time were investigated as per optimized response parameters.

IN-VITRO DISSOLUTION:

Table 19: In-vitro dissolution of core tablets

Time (mins)	Cumulative drug release (%)				
	Trial-1	**Trial-2**	**Trial-3**	**Trial-4**	**Trial-5**
5	40.31	76.50	81.15	95.21	97.31
10	41.75	77.54	81.24	96.56	97.97

15	41.90	78.56	87.91	97.58	98.30
20	42.15	78.45	88.64	98.26	98.95
30	43.45	79.20	89.70	99.27	99.93
45	45.17	80.20	90.21	99.95	99.95

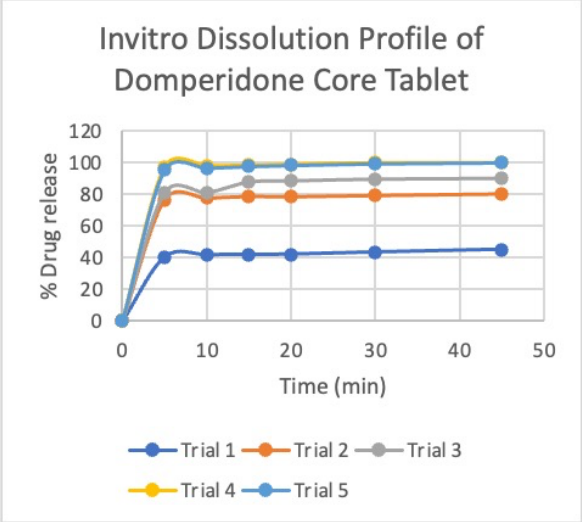


Fig 14: % drug release of core tablet

The dissolution profiles of the Domperidone core tablet were studied in 0.1 HCL. The drug releases of the formulation trials were determined. The cumulative drug releases for formulation trails were found within the range of 96.56 % to 99.95%. The effects of independent variables on cumulative drug release were investigated as per optimized response parameters.

15. EVALUATION OF FLOATING PULSATILE RELEASE TABLET:

Table 20: Evaluation of FPRT

For mula					Fri abil
F1	297.5 ±0.02	4.09±0. 01	9.1±0. 05	14.52± 0.12	0.5 5
F2	302.3 ±0.05	4.62±0. 02	9.1±0. 02	19.12± 0.19	0.6 6
F3	299.7 ±0.02	4.66±0. 01	9.1±0. 01	17.50± 0.09	0.5 3
F4	300.2 ±0.05	4.68±0. 01	9.1±0. 02	19.92± 0.10	0.4 0
F5	298.6 ±0.02	4.65 ±0.05	9.1±0. 04	20.0±0 .10	0.5 0

Table 21: Evaluation of FPRT

Formulations	Floating lag time	Floating time (Hrs)
F1	6.2	5
F2	4.7	7
F3	6	9
F4	4	11
F5	5	8

For FPRTs characterization, total of 5 formulations containing varying concentrate ions 5 HPMC K100M and Ethyl cellulose were evaluated for thickness, diameter, hardness, friability, and drug release profile in terms of floating time and floating lag time. It was found that all FPRT formulations showed satisfactory features in terms of thickness, diameter and harness (table).

16. SWELLING INDEX:

Table 22: Swelling index of FPRT

Formulation Code	Swelling index (%)
F1	80.50 %
F2	85.72%
F3	87.73 %
F4	90.40%
F5	82.12%

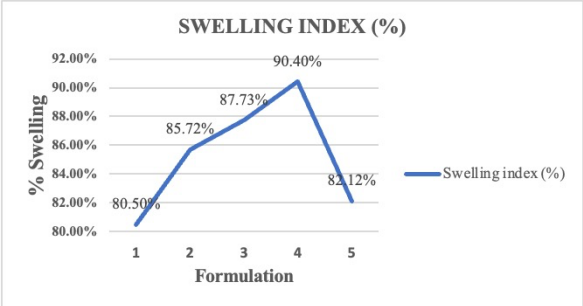


Fig 15: % of the swelling index of FPRT

The swelling behavior of optimized FPRTs containing HPMC K100M was compared with other FPRTs containing ethyl cellulose.

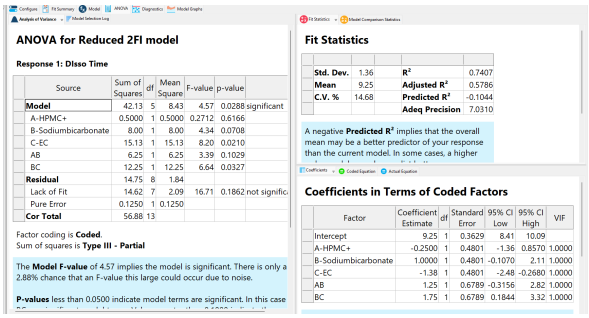
17. OPTIMIZATION:

Design Table:

Std	Run	Factor 1 A:HPMC+ Mg	Factor 2 B:Sodiumbicarb... Mg	Factor 3 C:EC Mg	Response 1 Dlsso Time Hrs	Response 2 Floating time Hrs	Response 3 Assay %
2	1	40	15	25	6	6	80
8	2	40	20	30	6.5	6.5	82
7	3	30	20	30	7	7	84
11	4	35	15	30	7.5	7.5	86
14	5	35	20	25	8	8	88
13	6	35	20	25	8.5	8.5	90
1	7	30	15	25	9	9	92
10	8	35	25	20	9.5	9.5	94
3	9	30	25	25	10	10	96
6	10	40	20	20	10.5	10.5	98
5	11	30	20	20	11	11	100
12	12	35	25	30	11.5	11.5	102
4	13	40	25	25	12	12	104
9	14	35	15	20	12.5	12.5	106

Fig 16: Design Table

18. 1ANOVA – I (Disso Time):



ANOVA for Reduced 2FI model

Response 1: DIsso Time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	42.13	5	8.43	4.57	0.0288	significant
A-HPMC+	0.5000	1	0.5000	0.2712	0.6166	
B-Sodiumbicarbonate	8.00	1	8.00	4.34	0.0708	
C-EC	15.13	1	15.13	8.20	0.0210	
AB	6.25	1	6.25	3.39	0.1029	
BC	12.25	1	12.25	6.64	0.0327	
Residual	14.75	8	1.84			
Lack of Fit	14.62	7	2.09	16.71	0.1862	not significa
Pure Error	0.1250	1	0.1250			
Cor Total	56.88	13				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 4.57 implies the model is significant. There is only a 2.88% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case

Fit Statistics

Std. Dev.	1.36	**R²**	0.7407
Mean	9.25	**Adjusted R²**	0.5786
C.V. %	14.68	**Predicted R²**	-0.1044
		Adeq Precision	7.0310

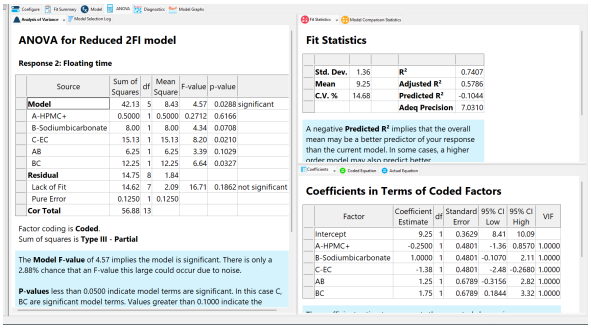
A negative **Predicted R²** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	9.25	1	0.3629	8.41	10.09	
A-HPMC+	-0.2500	1	0.4801	-1.36	0.8570	1.0000
B-Sodiumbicarbonate	1.0000	1	0.4801	-0.1070	2.11	1.0000
C-EC	-1.38	1	0.4801	-2.48	-0.2680	1.0000
AB	1.25	1	0.6789	-0.3156	2.82	1.0000
BC	1.75	1	0.6789	0.1844	3.32	1.0000

Fig 17: ANOVA for Reduced 2FI model of In-vitro Dissolution

18.1. ANOVA – II (Floating Time):



ANOVA for Reduced 2FI model

Response 2: Floating time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	42.13	5	8.43	4.57	0.0288	significant
A-HPMC+	0.5000	1	0.5000	0.2712	0.6166	
B-Sodiumbicarbonate	8.00	1	8.00	4.34	0.0708	
C-EC	15.13	1	15.13	8.20	0.0210	
AB	6.25	1	6.25	3.39	0.1029	
BC	12.25	1	12.25	6.64	0.0327	
Residual	14.75	8	1.84			
Lack of Fit	14.62	7	2.09	16.71	0.1862	not significant
Pure Error	0.1250	1	0.1250			
Cor Total	56.88	13				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 4.57 implies the model is significant. There is only a 2.88% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case C, BC are significant model terms. Values greater than 0.1000 indicate the

Fit Statistics

Std. Dev.	1.36	**R²**	0.7407
Mean	9.25	**Adjusted R²**	0.5786
C.V. %	14.68	**Predicted R²**	-0.1044
		Adeq Precision	7.0310

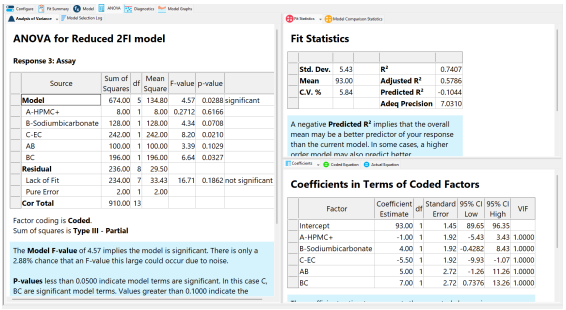
A negative **Predicted R²** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	9.25	1	0.3629	8.41	10.09	
A-HPMC+	-0.2500	1	0.4801	-1.36	0.8570	1.0000
B-Sodiumbicarbonate	1.0000	1	0.4801	-0.1070	2.11	1.0000
C-EC	-1.38	1	0.4801	-2.48	-0.2680	1.0000
AB	1.25	1	0.6789	-0.3156	2.82	1.0000
BC	1.75	1	0.6789	0.1844	3.32	1.0000

Fig 18: ANOVA for Reduced 2FI model of Floating Time

18.2. ANOVA – III (Assay):



ANOVA for Reduced 2FI model

Response 3: Assay

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	674.00	5	134.80	4.57	0.0288	significant
A-HPMC+	8.00	1	8.00	0.2712	0.6166	
B-Sodiumbicarbonate	128.00	1	128.00	4.34	0.0708	
C-EC	242.00	1	242.00	8.20	0.0210	
AB	100.00	1	100.00	3.39	0.1029	
BC	196.00	1	196.00	6.64	0.0327	
Residual	236.00	8	29.50			
Lack of Fit	234.00	7	33.43	16.71	0.1862	not significant
Pure Error	2.00	1	2.00			
Cor Total	910.00	13				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 4.57 implies the model is significant. There is only a 2.88% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case C, BC are significant model terms. Values greater than 0.1000 indicate the

Fit Statistics

Std. Dev.	5.43	**R²**	0.7407
Mean	93.00	**Adjusted R²**	0.5786
C.V. %	5.84	**Predicted R²**	-0.1044
		Adeq Precision	7.0310

A negative **Predicted R²** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	93.00	1	1.45	89.65	96.35	
A-HPMC+	-1.00	1	1.92	-5.43	3.43	1.0000
B-Sodiumbicarbonate	4.00	1	1.92	-0.4282	8.43	1.0000
C-EC	-5.50	1	1.92	-9.93	-1.07	1.0000
AB	5.00	1	2.72	-1.26	11.26	1.0000
BC	7.00	1	2.72	0.7376	13.26	1.0000

Fig 19: ANOVA for Reduced 2FI model of Assay

Constraints:

Constraints

	Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
	A:HPMC+	is in range	30	40	1	1	3
	B:Sodiumbicarbonate	is in range	15	25	1	1	3
	C:EC	is in range	20	30	1	1	3
	DIsso Time	is target = 9.25	6	12.5	1	1	3
	StdErr(DIsso Time)	minimize	0.3629	1.02644	1	1	3
	Floating time	is target = 9.25	6	12.5	1	1	3
	StdErr(Floating time)	minimize	0.3629	1.02644	1	1	3

Fig 20: Selection of appropriate constraints by StatEase software

Design Table:

Constraints

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:HPMC+	is in range	30	40	1	1	3
B:Sodiumbicarbonate	is in range	15	25	1	1	3
C:EC	is in range	20	30	1	1	3
DIsso Time	is target = 9.25	6	12.5	1	1	3
StdErr(DIsso Time)	minimize	0.3629	1.02644	1	1	3
Floating time	is target = 9.25	6	12.5	1	1	3
StdErr(Floating time)	minimize	0.3629	1.02644	1	1	3
Assay	is target = 93	80	106	1	1	3
StdErr(Assay)	minimize	1.4516	4.10575	1	1	3

Solutions

8 Solutions found

Number	HPMC+	Sodiumbicarbonate	EC	Disso Time	StdErr(Disso Time)	Floating time	StdErr(Floating time)	Assay	StdErr(Assay)	Desirability	
1	**35.000**	**20.000**	**25.000**	**9.250**	**0.363**	**9.250**	**0.363**	**93.000**	**1.452**	**1.000**	**Selected**
2	35.011	20.038	25.026	9.250	0.363	9.250	0.363	93.000	1.452	1.000	
3	34.998	19.959	24.971	9.250	0.363	9.250	0.363	93.000	1.452	1.000	
4	34.936	19.984	25.000	9.250	0.363	9.250	0.363	93.000	1.452	1.000	
5	34.956	20.038	25.036	9.250	0.363	9.250	0.363	93.000	1.452	1.000	
6	35.070	20.033	25.012	9.250	0.363	9.250	0.363	93.000	1.452	1.000	
7	34.901	19.905	24.952	9.250	0.363	9.250	0.363	93.000	1.453	1.000	
8	35.059	20.116	25.077	9.250	0.363	9.250	0.363	93.000	1.453	1.000	

Fig 21: Design Table (Constraints & Solutions)

Contour Plot: Desirability

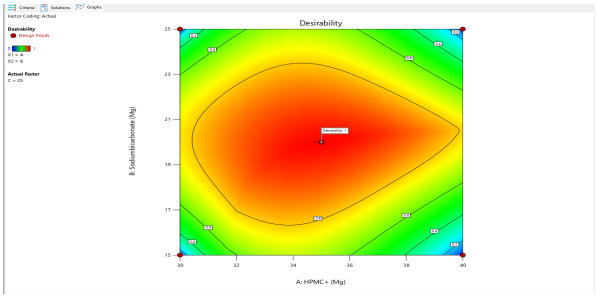


Fig 22: Contour Plot: Desirability

Contour plot of all factors:

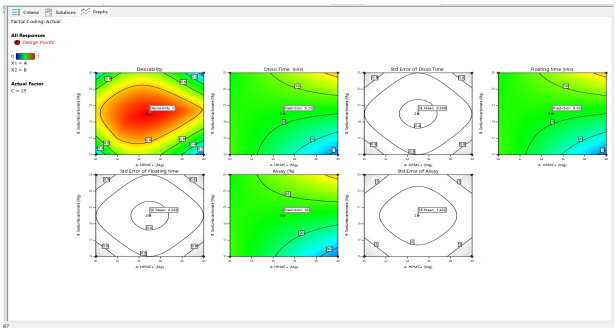
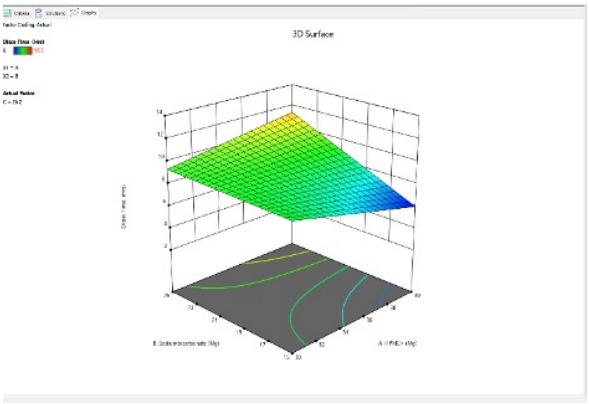


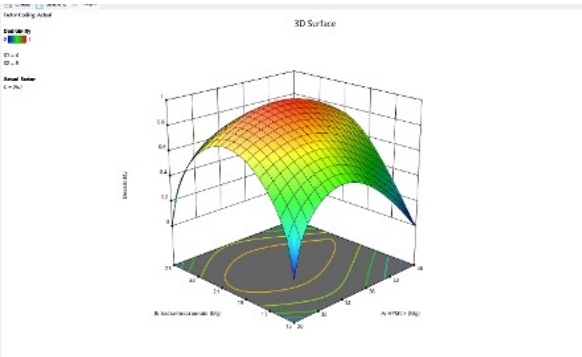
Fig 23: Contour plot of all factors



3D Interpretation plot: Desirability

Fig 24: 3D Interpretation plot: Desirability

3D Interpretation plot: Dissolution time



3D Interpretation plot: Floating Time

3D Interpretation plot: Assay

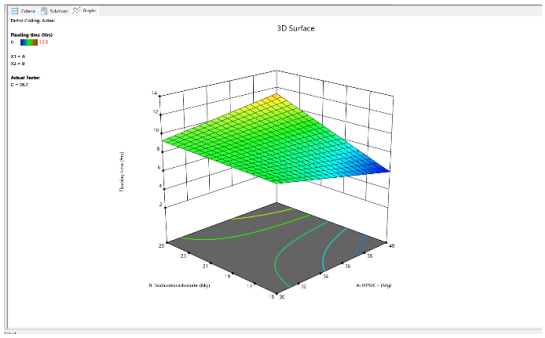


Fig 25: 3D Interpretation plot: Floating Time

19. ASSAY BY HPLC METHOD:

Table 23: Assay by HPLC method of FPRTs

Formulation code	Floating lag time (mins)	Total Floating time (hours)	Assay by HPLC Method (Drug content (%))
F1	6.2	5	95.88
F2	4.7	7	93.26
F3	6	9	96.75
F4	4	11	100.10
F5	5	8	98.23

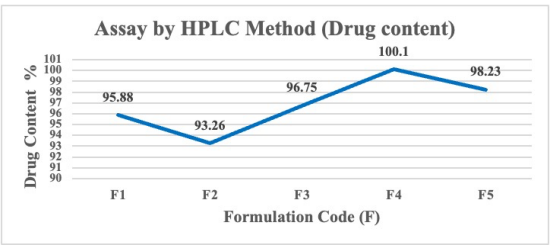
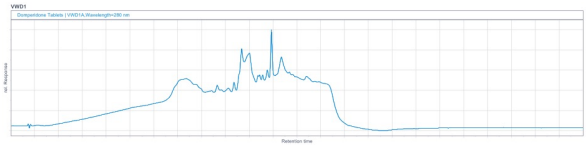
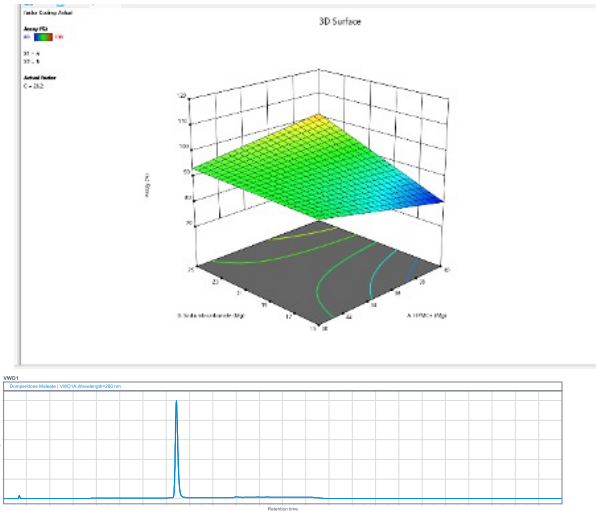


Fig 26: Assay by HPLC method of FPRTs

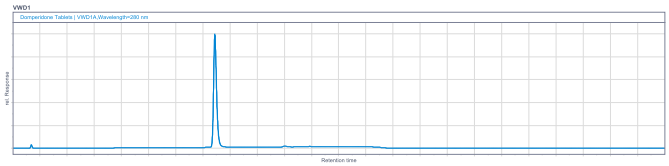
Blank



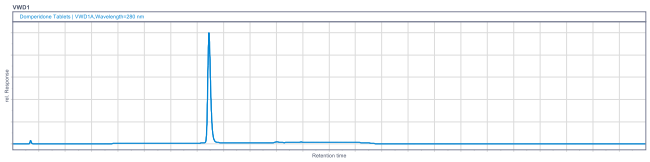
Standard Chramtogram



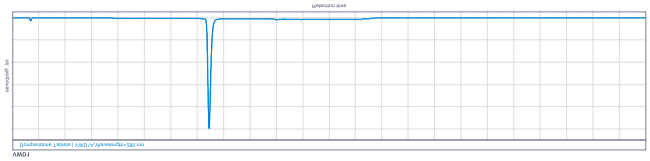
Sample 1



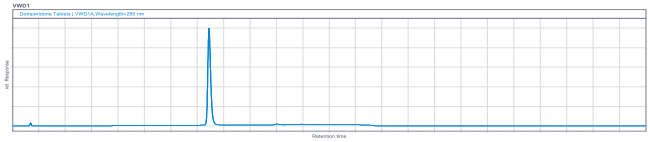
Sample 2



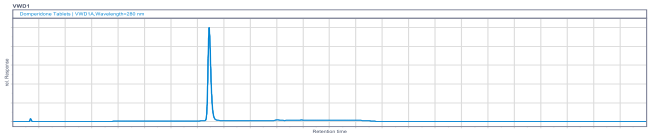
Sample 3



Sample 4



Sample 5



20. IN-VITRO DISSOLUTION OF FPRT:

Table 24: In-vitro dissolution by UV method of FPRTs

Time (mins)	F1	F2	F3

30	0	0	0	0	0	0
60	0	0	0	0	0	0
120	0	0	0	0	0	0
180	36.13	0	0	0	0	0
240	77.60	0	0	0	0	0
300	97.00	0	0	0	0	0
360	97.23	0	0		38.11	32.50
420		2.17	3.14		45.17	36.56
480		2.40	3.47		64.56	50.32
540		4.95	6.41		75.02	67.82
600		6.27	7.32		87.63	83.24
660		10.90	8.09		100.71	92.13

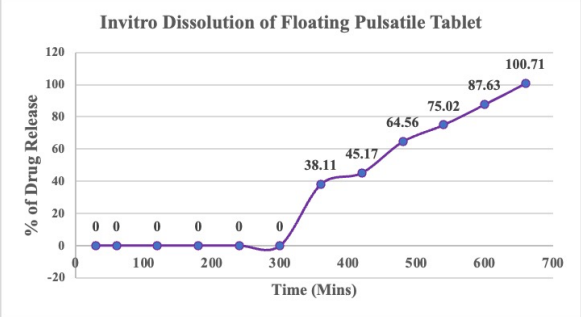


Fig 27: In-vitro Dissolution of FPRTs

21. STABILITY STUDIES:

Stability studies were carried out of the optimized formulation (F4) at 40 ± 2 ºC & 75 ±5 % RH for 30 days as per ICH guidelines. At various time intervals (initial &30 days). The samples were evaluated for thickness (mm), Diameter (mm), Hardness (kg/cm^2), drug release (%), and floating lag time. There was no major change in the evaluation parameters. The results are shown in the table.

Table 25: Stability studies of FPRTs

Parameters	**Storage conditions 40 ± 20 ºC**	
	Initial	**30 days**
Appearance	No change	No change
Average weight	300.2	300.7
Thickness	4.68	4.69
Diameter	9.1	9.1
Hardness	19.92	19.92
Drug release	100.10	100.10
Floating lag time	4	4

22. CONCLUSION

The study was concluded to develop a controlled floating pulsatile release tablets of Domperidone by wet granulation method for prolonged gastric residence time and to increase the bioavailability of the drug. All the formulations (F1-F5) were optimized by using design expert software by CCD and the optimized batch was found to be F4. The formulated tablets were found to be within the limits with respect to uniformity of weight, hardness, thickness, friability, drug content, floating lag time, floating time and swelling index. The in-vitro dissolution studies of F4 showed maximum drug release of 100.71%.

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